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Practitioner's Docket No. U 013963-9 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Dilip G. **SAOJI**, et al.
Serial No.: 10/749,931 Group No.: 1614
Filed: December 31, 2003 Examiner:
For: COMPOSITIONS OF BENZOQUINOLIZINE CARBOXYLIC ACID ANTIBIOTIC DRUGS

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF CERTIFIED COPY

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country: INDIA

Application Number: 1169/MUM/2002

Filing Date: December 31, 2002

WARNING: "When a document that is required by statute to be certified must be filed, a copy, including a photocopy or facsimile transmission of the certification is not acceptable." 37 C.F.R. 1.4(f) (emphasis added).

CERTIFICATE OF MAILING (37 C.F.R. 1.8a)

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Date: May 20, 2004

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(type or print name of person certifying)

SIGNATURE OF PRACTITIONER

Reg. No.: 33,778

JANET I. CORD
(type or print name of practitioner)

Tel. No.: (212) 708-1935

LADAS & PARRY
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NOTE: "The claim to priority need be in no special form and may be made by the attorney or agent, if the foreign application is referred to in the oath or declaration, as required by § 1.63." 37 C.F.R. 1.55(a).

U013963-9
S.N.: 10/749,931
Group No. 1614

INTELLECTUAL PROPERTY **INDIA**
PATENTS / DESIGNS / TRADE MARKS/ GEOGRAPHICALINDICATIONS

सत्यमेव जयते

Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

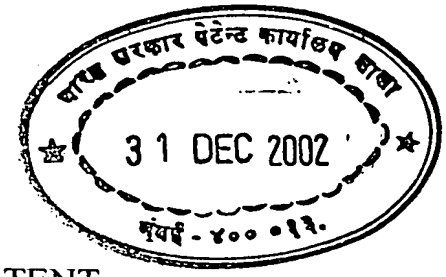
IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional specification filed on 31/12/2002 in respect of Patent Application No. 1169/MUM/2002 of Wockhardt Limited , Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai – 400 051, Maharashtra State, India, an Indian Company registered under the Companies Act, 1956.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

Dated this 19th day of March 2004.

(N.K. GARG)
ASST. CONTROLLER OF PATENTS & DESIGNS.

FORM 1



THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

[See sections 5(2), 7, 54 and 135 and rule 33A]

1. We, Wockhardt Limited, Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, Maharashtra State, India an Indian Company registered under the Companies Act 1956

2. hereby declare:-

ORIGINAL

a) that we are in possession of an invention titled 'A Process for Solution Compositions of Benzoquinolizine Carboxylic Acid Antibiotic Drugs'

b) that the Provisional Specification relating to this invention is filed with this application.

c) that there is no lawful ground of objection to the grant of a patent to us.

3. further declare that the inventor (s) for the said invention are:

   a) Dr. Noel J de Souza

   b) Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, Maharashtra State, India.

   c) Indian National

4. We, claim the priority from the application(s) filed in convention countries, particulars of which are as follows :

   Not applicable

5. I/We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which I/we are the applicant/patentee:

   Not applicable.

6. I/We state that the application is divided out of my/our application, the particulars of which are given below and pray that this application deemed to have been filed on ____ under section 16 of the Act.

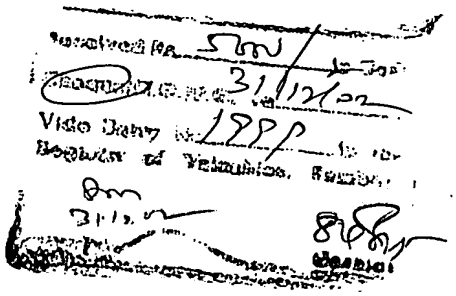
   Not applicable.

7. That we are the assignee or legal representative of the true and first inventors.

1169/mum/2002

31 DEC 2002 31/12/2002

1169/MUM/2002



8. That our address for service in India is as follows:

Wockhardt Limited
Wockhardt Towers
Bandra-Kurla Complex
Bandra (E)
MUMBAI 400 051
Tel. No. 022-6534444
Fax 022-6534242

9. Following declaration was given by the inventor(s):

We the true and first inventors for this invention declare that the applicant Wockhardt Limited, Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai 400 051 herein is our assignee.

Dr. Noel J de Souza _____

Dated this 30th day of December 2002

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Following are the attachment with the application:

a) Provisional specification – 3 copies
b) Form 2
c) Form 3

We request that a patent may be granted to us for the said invention.

Dated this 30th day of December 2002

DR N J de SOUZA
DIRECTOR-R&D

To

The Controller of Patents,
The Patents Office Branch, Mumbai.

भारत सरकार पेटेन्ट कार्यालय शाखा
31 DEC 2002
मुंबई-४०० ०१३.

FORM 2

THE PATENTS ACT, 1970
(39 of 1970)

PROVISIONAL SPECIFICATION
(See section 10)

1. Title: 'A PROCESS FOR'SOLUTION COMPOSITIONS OF BENZOQUINOLIZINE CARBOXYLIC ACID ANTIBIOTIC DRUGS'

2. Wockhardt Limited, Wockhardt Towers, Bandra Kurla Complex, Bandra (East) Mumbai – 400 051, Maharashtra State, India, an Indian Company registered under the Companies Act 1956

The following specification describes the nature of the invention and the manner in which it is to be performed.

ORIGINAL

A PROCESS FOR SOLUTION COMPOSITIONS OF BENZOQUINOLIZINE CARBOXYLIC ACID ANTIBIOTIC DRUGS

ABSTRACT:

The present invention relates to a pharmaceutical composition for therapeutic or prophylactic administration to a subject having an infective disease or condition at risk thereof. The composition comprising an aqueous carrier having in solution therein (a) a benzoquinolizine-2-carboxylic acid antimicrobial drug, in particular S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid, S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate or S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms, enantiomeric forms, other isomeric and racemic forms thereof, in a therapeutically or prophylactically effective drug concentration that is above the practical limit of solubility of the drug in a substantially isotonic aqueous solution at a physiologically compatible pH, and (b) a pharmaceutically acceptable solubilising agent, such an agent being a basic amino-acid or a cyclodextrin, or both a basic aminoacid and a cyclodextrin, in a concentration sufficient to maintain the drug in solution at such a drug concentration. The composition is particularly useful for intravenous delivery of the drug, both as ready to use injection and/or infusion solutions and dosage forms which can be converted into such injection and/or infusion solutions before use.

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition in aqueous solution form useful for oral, parenteral or topical application to a subject for treatment or prevention of infective disease. In particular the present invention relates to such a composition having an active agent a benzoquinolizine-2-carboxylic acid antibiotic drug. The field of the invention also includes processes for the preparation of such a composition, the use of such a composition in preparation of a medicament, and to the therapeutic or prophylactic use of such a composition.

ORIGINAL

BACKGROUND OF THE INVENTION

Achiral and chiral benzoquinolizine-2-carboxylic acid compounds have been reported to have therapeutically and/or prophylactically useful antibiotic or antimicrobial, in particular antibacterial, effects. Among such compounds are those illustratively disclosed in the following patents/applications, each of which is individually incorporated herein by reference.

US Patent No. 4,399,134

US Patent No. 4,552,879

EP Patent No. 9,081,81

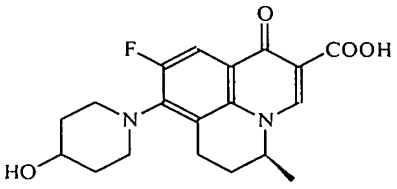
US Application No. 09/566,875

US Application No. 09/640,947

US Application No. 09/802,793

US Application No. 09/850,669

Compounds disclosed in some of the above cited US Patents include for example the compound 9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid, also known as nadifloxacin. Compounds of special relevance to this invention which are referred to herein are for instance compounds disclosed in the above cited US patent applications and correspond to S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate and, S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof. S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid has the structure shown in Formula I.



Formula I

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate, S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof, and in general benzoquinolizine-2-carboxylic acids exhibit strong antibacterial activity against sensitive and resistant strains of gram-positive organisms including those of the following genera: *Staphylococcus* (e.g.,

Staphylococcus aureus, Staphylococcus epidermidis), *Streptococcus* (e.g., *Streptococcus viridans, Streptococcus pneumoniae*), *Enterococcus* (e.g., *Enterococcus faecalis, Enterococcus faecium)*, anaerobes *Bacillus, Corynebacterium Chlamydia* and *Neisseria,* newly-emerging gram-negative organisms such as *Chryseobacterium meningosepticum* and *C. indologense*, gram-negative pathogens such as *E.coli*, Klebsiella, Proteus, Serratia, Citrobacter and Pseudomonas. The benzoquinolizine-2-carboxylic acid compounds of the invention are also generally effective against anaerobic organisms such as those of the genera Bacteroides and Clostridia, and against acid-fast organisms such as those of the genus Mycobacterium such as *Mycobacteria tuberculosis*, *M. intracellulare, M. avium,*

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid, bearing as it does a 4-hydroxypiperidine moiety as an 8-position substituent in the benzoquinolizine-2-carboxylic acid core, has a pKa value of 6.8. It or its 0.2 hydrate does not form, or does not readily form, acid addition salts. In US Patent 4,399,134 and US Patent 4,552,879, however, state that the described benzoquinolizine-2-carboxylic acid can be converted into a corresponding carboxylate salt with a pharmceutically acceptable basic compound by using alkali hydroxides and organic bases. The accompanying examples in US Patent 4,399,134 and US Patent 4,552,879 and also EP Patent No. 9,081,81 imply the use of a sodium salt of a benzoquinolizine carboxylic acid without the actual description of its preparation or of its physicochemical properties. The present inventors have shown that S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid and its 0.2 hydrate thereof does however, form base addition salts with basic amino acids used as counterions. Patent applications 09/802,793 and 10/156,685 disclose, in particular, the different polymorphic forms of S-(-)-9-

fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof. It is generally difficult to formulate a benzoquinolizine-2-carboxylic acid, S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate or S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof as a solution in a pharmaceutically acceptable liquid carrier, particularly in aqueous carrier, in view of their relatively low solubility in water. In the case of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate, for example, the solubility at ambient temperature is less than 0.1 mg/ml. In the case of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof, for example, the solubility at ambient temperature is less than 1.5 mg/ml.

The above-cited US Patent applications 09/566,875, 09/640,947, 09/802,793, 09/850,669 and 10/156,685 disclose that the subject antibiotic benzoquinolizine-2-carboxylic acids, and in particular S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate and different S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salts and polymorphic forms thereof, can be formulated as liquid form compositions including solutions. For example, it is disclosed in 09/566,875, 09/640,947, 09/802,793, 09/850,669 and 10/156,685 that the subject benzoquinolizine carboxylic acid compounds can be administered orally, rectally, parenterally, transdermally and/or topically and that parenteral administration can be by intravenous injection, infusion or other parenteral route.

For parenteral administration, it is disclosed that a suitable composition will generally contain a pharmaceutically acceptable amount of the subject benzoquinolizine carboxylic acid compound dissolved in a liquid carrier or diluent such as water for injection to form a suitably buffered isotonic solution. In US application 09/566,875, 09/640,947, 09/850,669 a specific embodiment of this invention utilises arginine as an excipient in the compositions to facilitate the aqueous solubility of the benzoquinolizine-2-carboxylic acid compounds.

Particularly where parenteral or oral administration of a benzoquinolizine-2-carboxylic acid, S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate or S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof drug is contemplated, it is desired to achieve systemic concentrations of the drug in the bloodstream above a minimum inhibitory concentration for 90% of a target organisms (MIC_{90}). It will readily be understood that it is difficult to achieve such concentrations by administration of a relatively small volume of a composition wherein the drug is present in dissolved form, unless the composition has a relatively high drug concentration, and in particular a drug concentration substantially above the limit of solubility in water of most benzoquinolizine-2-carboxylic acids and in particular of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate or S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof.

A need therefore exists for a solution composition of a benzoquinolizine-2-carboxylic acid, or S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate or S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof drug having a drug concentration substantially in excess of the practical limit of solubility of the drug in water. A particular need exists for a parenterally deliverable solution composition of a benzoquinolizine-2-carboxylic acid, S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid 0.2 hydrate or S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof drug having a relatively high concentration of the drug.

Some quinolone carboxylic acid are known to cause vain irritation upon infusion and accordingly, adversely affect the use of these compounds for parenteral administration to patients. However, solutions of benzoquinolizine carboxylic acid that reduce vain irritation and even phlebitis and are suitable for administration to human or veterinary patients have not been reported in the literature, except in the copending US applications of the current inventors.

SUMMARY OF THE INVENTION

The present invention provides a stable pharmaceutical composition suitable for therapeutic or prophylactic administration to a subject having or at risk of infective disease, the

composition, ready for use, or before administration converted into a composition of this type, comprising an aqueous carrier having in solution therein (a) a benzoquinolizine-2-carboxylic acid, or S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate or S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof antimicrobial drug in a therapeutically or prophylactically effective drug concentration that is above the practical limit of solubility of the drug in a substantially isotonic aqueous solution at a physiologically compatible pH, e.g. pH between (6.0 - 9.9) and (b) a pharmaceutically acceptable solubilising agent, such an agent being a basic amino-acid or a cyclodextrin or both a basic aminoacid and a cyclodextrin, in a concentration sufficient to maintain the drug in solution at such a drug concentration. Preferably the drug concentration is in a range of about 1 to about 100 mg/ml. The term "stable" in the present context encompasses compositions stable to light under the normal conditions for use and stable to temperature while having a pH compatible with direct administration.

The term "suitable for therapeutic or prophylactic administration" in the present context encompasses compositions such as injection solutions or infusion solutions that are suitable for direct administration as formulated, compositions that are suitable for administration upon dilution in an appropriate pharmaceutically acceptable liquid, and also other presentations which before administration are converted into injection solutions or infusion solutions of this type. Where the composition is intended for direct administration as formulated, the drug concentration is more preferably about 1 to about 20 mg/ml and most preferably about 4 to about 12 mg/ml.

Investigation by the inventors of pH-solubility profile of the benzoquinolizine-2-carboxylic acid with different counterions to provide a stable solution dosage form, which would reduce vain irritation and phlebitis and would also comply with safety requirements of drug regulatory authorities, such as abnormal toxicity, led the inventors to the choice of a pharmaceutically acceptable basic amino-acid. Although use of a basic amino acid is known in the art (US Patent Nos. 3,676,434, 3,708,478) to form solutions of B-Lactam antibiotic drugs, such a choice has been shown in our cited copending applications for the first time for benzoquinolizine-2-carboxylic acids.

Use by the inventors of counterions tried other than amino acid like for instance sodium described in US Patent 4,399,134 and US Patent 4,552,879 and also EP Patent No. 9,081,81 fail in respect of providing a solution with one or more of the following requirements such as been devoid of phlebitogenic properties, or free of abnormal toxicity or in remaining sufficiently stable, for utility as a marketable parenteral drug. The present invention is based in part on the establishment that addition of an amount of amino acid, in particular of the amino acid arginine, in a prescribed range provides to a surprising degree a solution with (a) increased solubility of benzoquinolizine-2-carboxylic acid (b) lowered potential to induce phlebitogenicity (c) fulfilling the abnormal toxicity regulatory requirements and (d) stability when stored for an extended period at specified temperature and humidity ranges. These attributes, among other benefits, make it possible for the first time to deliver intravenously a therapeutically or prophylactically effective dose of the benzoquinolizine-2-carboxylic acid, S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid, S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-

yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate or S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof in a volume small enough to be clinically acceptable and convenient, even for subjects intolerant of large volume intravenous infusion because of hypertension, cardiac, renal and/or other problems. For example, a 900 mg dose of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof can, through use of a composition of the present inventions be delivered intravenously in a volume of 100 ml or less.

Similar investigations by the inventors also led them to the choice of an appropriate cyclodextrin for enhancing the solubility of the drugs of the invention. It is believed, without being bound by theory, that the enhanced solubility of the drug in a composition of the invention is due to association of at least a portion of the drug with the cyclodextrin. It is further believed that at least one mechanism by which the drug associates with the cyclodextrin compound to enhance solubility of the drug in an aqueous medium is through formation of an inclusion complex. The cyclodextrin complex may be formed with the unionized acidic drug itself or with the salt of the acidic drug. Such complexes or conjugates are known in the art to form with a variety of drugs, and a number of advantages have been postulated for use of cyclodextrin-drug complexes in pharmacy. See for example review articles by Bekers et al. (1991) in Drug Development and Industrial Pharmacy, 17, 1503-1549, Szejtli (1994) in Medical Research Reviews, 14, 353-386; Zhang & Rees (1999) in Export Opinion on Therapeutic Patents, 9,1697-1717; and Redenti et al, (2001) in J. Pharm. Sci., 90, 979 – 986.

Formulations of various drugs with various cyclodextrins have been proposed in the patent literature, including the patents and publications referenced below.

US Patent No. 5,670,530 discloses compositions comprising a rhodacyanine anti-cancer agent and a cyclodextrin.

US Patent No. 5,756,546 discloses compositions comprising nimesulide and a cyclodextrin.

US Patent No. 5,807,895 discloses compositions comprising a prostaglandin and a cyclodextrin.

US Patent No. 5,824,668 discloses compositions comprising a 5β steroid drug and a cyclodextrin.

International Patent Publication No. WO 96/32135 discloses compositions comprising propofol and a cyclodextrin.

International Patent Publication No. WO 96/38175 discloses compositions comprising an antiulcerative benzimidazole compound and a branched cyclodextrin-carboxylic acid.

International Patent Publication No. WO 97/39770 discloses compositions comprising a thrombin inhibitor and a cyclodextrin.

International Patent Publication No. WO 98/37884 discloses compositions comprising a 3,4-diarylchroman compound and a cyclodextrin.

International Patent Publication No. WO 98/55148 discloses compositions comprising a sparingly water-soluble drug, a cyclodextrin, a water-soluble acid and a water-soluble organic polymer.

International Patent Publication No. WO 98/58677 discloses compositions comprising voriconazole and a cyclodextrin.

International Patent Publication No. WO 99/2073 discloses compositions comprising a taxoid such as paclitaxel or docetaxel and a cyclodextrin.

International Patent Publication No. WO 99/27932 discloses compositions comprising an antifungal compound of defined formula and a cyclodextrin.

International Patent Publication No. WO 01/82971 discloses compositions comprising a glycopeptide antibiotic and a cyclodextrin.

International Patent Publication No. WO 02/15940 discloses compositions comprising an oxazolidinone antimicrobial drug and a cyclodextrin.

International Patent Publication No. WO 02/47660 discloses compositions comprising dronedarone and a cyclodextrin.

However, the degree of enhancement of solubility achievable through complexation with cyclodextrins of a particular drug or class of drugs is not generally predictable. Cyclodextrins are expensive excipients and in many cases the degree of enhancement of solubility, or other benefit obtained, has not economically justified the increased cost of a formulation arising from addition of a cyclodextrin. The present invention is based in part on the discovery that addition of a relatively modest amount of cyclodextrin compound increases the solubility of a benzoquinolozine-2-carboxylic acid antibiotic drug or its salt with a basic amino acid to a surprising degree. The enhancement in solubility, among other benefits, makes it possible for the first time to deliver intravenously a therapeutically or prophylactically effective dose of the benzoquinolizine-2-carboxylic acid or its salt with a basic amino acid in a volume small enough to be clinically acceptable and convenient, even for subjects intolerant of large volume intravenous infusion because of hypertension, cardiac, renal and/or other problems. For example, a 900 mg dose of S-(-)-9-fluoro-6,7-dihydro-8-(4-

hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof can, through use of a composition of the present invention, be delivered intravenously in a volume of 100 ml or less.

The term "pharmaceutically acceptable" in relation to an amino acid or cyclodextrin or other excipient herein means having no persistent detrimental effect on the health of the subject being treated. The pharmaceutical acceptability of an amino acid or cyclodextrin depends, among other factors, on the particular amino acid or cyclodextrin compound in question, on its concentration in the administered composition, and on the route of administration.

For example use of arginine, in particular L-arginine, as a counterion is not limited generally.

The term "practical limit of solubility" in relation to a drug means the highest concentration at which the drug can be formulated in solution without risk of precipitation or crystallization of the drug during the normal range of manufacturing, packaging, storage, handling and use conditions. Typically the practical limit of solubility is considerably lower than the true solubility limit in a given aqueous medium, for example about 70% of the true solubility limit. Thus, illustratively, for a drug having a true solubility limit in a given aqueous medium of 2.9 mg/ml, the practical limit of solubility is likely to be about 2 mg/ml.

Except where the context demands otherwise, use of the singular herein will be understood to embrace the plural. For example, by indicating above that a composition of the invention comprises "a benzoquinolizine-2-carboxylic acid antibiotic drug" and "a pharmaceutically acceptable aminoacid or both a basic aminoacid and a cyclodextrin compound", it will be

understood that the composition can contain one or more such drugs and one or more such aminoacids and/or cyclodextrin compounds.

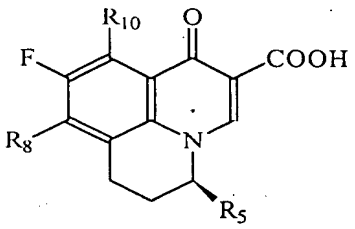
The invention also provides a method of preparing a medicament for treating or preventing infective disease, using a composition as described above.

Also embraced by the present invention is a method of treating or preventing infective disease in a subject, the method comprising administration to the subject of a composition as described above in a therapeutically or prophylactically effective dose. Such administration can be oral, parenteral or topical, but is preferably parenteral and more preferably by intravenous injection or infusion.

The method of the invention is particularly useful where the infective disease arises through infection by one or more gram-positive bacteria, for example those of the genera Staphylococcus (e.g., *Staphylococcus aureus, Staphylococcus epidermidis*), Streptococcus (e.g., *Streptococcus viridans, Streptococcus pneumoniae*), *Enterococcus* (e.g., *Enterococcus faecalis, Enterococcus faecium)*, Bacillus, Corynebacterium, Chlamydia and Neisseria, anaerobic organisms, for example those of the genera Bacteroides and Clostridia, and acid-fast organisms, for example those of Mycobacterium. The method of the invention is especially useful where infection is by a strain of gram-positive bacteria that is resistant to fluoroquinolone, B-lactam, macrolide, oxazolidinone antibiotics.

DETAILED DESCRIPTION OF THE INVENTION

Any benzoquinolizine-2-carboxylic acid, antimicrobial drug or one of its chiral isomers i.e. one having a benzoquinolizine-2-carboxylic acid moiety as part of its chemical structure, can be formulated with an amino acid or cyclodextrin compound or both a basic aminoacid and a cyclodextrin in accordance with the invention. Preferred benzoquinolizine-2-carboxylic acid are compounds having Formula-II.

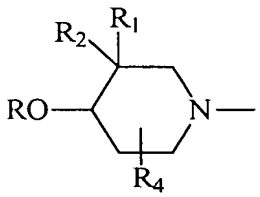


Formula-II

Preferably R_5 is C_{1-6} alkyl, and more preferably R_5=CH_3, in a stereochemical orientation which is preferably an S-orientation.

Preferably R_8 is 4-hydroxypiperidinyl optionally further substituted with one or more C_{1-6} alkyl, hydroxypiperidinyl optionally further mono/poly substituted with C_{1-6} alkyl.

More preferably R_8 is



wherein

R is hydrogen, or C_1-C_6 alkyl as hereinbefore defined, or glycosyl, or aralkyl such as benzyl, or C_1-C_6 alkanoyl such as acetyl, propionyl, pivaloyl, or aminoalkanoyl such as amino acid residues derived from one of the 20 naturally occurring amino acids viz. alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine, or the optically active isomers thereof, or the racemic mixtures thereof, or $C_6H_{11}O_6$, PO_3H_2 or SO_3H thus giving respectively the gluconic acid, phosphoric acid and sulfonic acid ester derivatives of the compounds.

R_1=R_2 = H, C_{1-4} alkyl, aralkyl, aminoalkyl, trifluoroalkyl, halogen,

R_4 = H, C_{1-4} alkyl, CF_3, phenyl, or F, R4 is present at one or more of the positions of 2-, 4-, 5-, or 6- of the piperidine ring;

R_{10} is H, C_{1-5} alkyl, amino, alkylamino, acylamino

or an optical isomer, diastereomer or enantiomer thereof, or polymorphs and pseudopolymorphs or prodrugs thereof or pharmaceutically acceptable salts and hydrates thereof.

"Optical isomer", "stereoisomer", and "diastereomer" as referred to herein have the standard art recognized meanings.

Examples of preferred benzoquinolizine-2-carboxylic acid are compounds selected from

RS-, R-, or S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid

RS-, R-, or S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof

RS-, R-, or S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid arginine salt 0.2 hydrate

S-(-)-9-fluoro-6,7-dihydro-8-{trans-4-(RS)-hydroxy-3-(RS)-methylpiperidin-1-yl}-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid,

S-(-)-9-fluoro-6,7-dihydro-8-{cis-4-(RS)-hydroxy-3-(RS)-methylpiperidin-1-yl-5-methyl-oxo-1H,5H-benzo[i, j]quinolizine-2-carboxylic acid,

S-(-)-9-fluoro-6,7-dihydro-8-{cis-(-)-4-R-hydroxy-3-S-methylpiperidin-1-yl}-5-methyl-1-oxo-1H,5H-benzo[i, j]quinolizine-2-carboxylic acid,

S-(-)-9-fluoro-6,7-dihydro-8-{cis-(+)-4-S-hydroxy-3-R-methylpiperidin-1-yl}-5-methyl-1-oxo-1H,5H-benzo[i, j]quinolizine-2-carboxylic acid,

S-(-)-9-fluoro-6,7-dihydro-8-(3-ethyl-4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid (mixture of cis racemate and trans racemate).

In a specially preferred embodiment the benzoquinolizine-2-carboxylic acid are S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof, S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 H_2O and S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid.

The invention is illustrated herein with particular reference to S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof will be understood that any other benzoquinolizine antimicrobial drug can, if desired, be substituted in whole or in part for S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof, with appropriate adjustment in concentration and dosage ranges, in the compositions and methods herein described.

Benzoquinolizine compounds used in compositions of the invention can be prepared by a process known per se, in the case of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof, for example, by process described in the following patents, each of which is individually incorporated herein by reference.

US Application No. 09/802,793

US Application No. 10/156,685

Other benzoquinolizine compounds can be prepared by processes known per se, including process set forth in patent publications disclosing such drugs.

US Application No. 09/566,875

US Application No. 09/640,947

US Application No. 09/850,669

US Patent No. 4,399,134

US Patent No. 4,552,879

In addition to the active compound, water and other customary formulating auxiliaries, the infusion solutions according to the invention preferably contain an amount, which suffices to dissolve the active compound and to stabilize the solution, of one or more basic amino acid(s) from the group comprising of L-arginine, L-histidine, L-arginine acetate, L-arginine-L-glutamate, L-arginine monohydrochloride, L-histidine acetate, L-histidine acetate dihydrate, L-histidine monohydrochloride, L-histidine monohydrochloride monohydrate, L-Lysine, L-Lysine acetate, L-Lysine monohydrochloride and /or their salts and/or D or DL forms of these amino acids.

L-arginine and L-lysine or mixtures of L-arginine and L-lysine are particularly preferred.

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof is usefully present in a composition of the invention at a concentration of about 1 mg/ml to as high a concentration as is practically enabled by the basic amino acid or the cyclodextrin or both the amino acid and the cyclodextrin present therewith, for example about 100 mg/ml. Preferably in a composition intended for direct administration as formulated, the concentration of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof is about 1 to about

10 mg/ml, more preferably about 4 to about 12 mg/ml, for example about 9 mg/ml. Preferably in a composition intended for dilution in a pharmaceutically acceptable liquid prior to administration, the concentration of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof is about 10 to about 150 mg/ml, more preferably about 40 to about 120 mg/ml, for example about 90 mg/ml. Useful concentrations of other benzoquinolizine drugs are those that are therapeutically equivalent to the S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof concentration ranges given immediately above.

Typically, where the composition is intended for direct administration as formulated, suitable concentrations of cyclodextrin will be found in a range from about 15 to 35 to about 25 mg/ml. Where the composition is intended for dilution prior to administration, the concentration of cyclodextrin can be significantly higher, for example about 150 to about 350 mg/ml.

One or more pharmaceutically acceptable pH adjusting agents and/or buffering agents can be included in a composition of the invention, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, citrate/phosphate, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an

amount required to maintain pH of the composition in a physiologically acceptable range, particularly where the composition is intended for parenteral delivery.

One or more pharmaceutically acceptable salts or other solutes can be included in the composition in an amount required to bring osmolality of the composition into a physiologically acceptable range, particularly where the composition is intended for parenteral delivery. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; preferred salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate, with sodium chloride being especially preferred. Other solutes suitable for adjustment of osmolality include sugars, for example dextrose.

Accordingly, a particular embodiment of the invention is a composition as described hereinabove, further comprising a buffering agent and/or an agent for adjusting osmolality in amounts whereby the solution is substantially isotonic and has a physiologically acceptable pH.

Other pharmaceutically acceptable excipients can also be as desired in compositions of the invention, having functions conventional in the art and in amounts consistent with those functions. For example, a water-soluble organic solvent can be included if desired, as disclosed in U S Patent No. 5,486,508 to Nishida et al., which contemplates a composition suitable for injection comprising a slightly water-soluble drug, a cyclodextrin and a water-soluble organic solvent.

The compositions according to the invention can be prepared by adding and dissolving following ingredients in water or vehicle system: active compound, one or more amino acid(s) or their salts and/or a cyclodextrin intended to ensure complete solubilization of active compound and / or the tonicity regulator and the other adjuvants.

The compositions according to the inventions are alternatively prepared by addition of water to a mixture comprising active compound, one or more amino acid(s) or their salts, and/or a cyclodextrin which suffices to dissolve the active compound, and to ensure complete solubilization of active compound, and / or the tonicity regulator and the other adjuvants. or else by the addition of active compound and if appropriate other additives such as to a solution of the amino acid(s) and/or a cyclodextrin.

However, the invention also relates to lyophilizates which have been prepared by customary techniques and which are converted into the infusion solutions according to the invention by dissolution in solvents suitable for this purpose-such as, for example, conventional infusion vehicle solutions. Lyophilizates of this type can be obtained by freeze-drying of various starting solutions such as, for example, the infusion solutions according to the invention. It is likewise possible to freeze-dry considerably more dilute solutions as well as considerably more concentrated solutions than the infusion solutions according to the invention.

The lyophilizates can be prepared both by freeze-drying in the final container such as, for example, in a bottle or ampoule made of glass or plastic, and by bulk freeze-drying combined with dispensing the lyophilizate into a container suitable for this purpose, which takes place at a later time.

The dissolution of the lyophilizate before the administration can be brought about both by addition of a solution, which is suitable for this purpose, into the container containing the lyophilizate, or by addition of the lyophilizate to a suitable solution, or by a combination of procedures of these types.

The composition of the lyophilizates can likewise vary very widely, depending on the composition of the solution which is used for the dissolution.

It can vary from pure active compound to a lyophilizate which contains all the constituents which are to be administered, apart from water.

The invention likewise relates compound to a lyophilizate with solutions containing active compound, which are converted into the infusion solutions according to the invention before the administration.

The invention also includes, powder for reconstitution which have been prepared by customary techniques and which are converted into the infusion solutions according to the invention by dissolution in solvents suitable for this purpose-such as, for example, conventional infusion vehicle solutions.

The powder for reconstitution can be prepared by blending active compound which has been recrystallised in advance under an aseptic condition, in an aseptic environment, with additives like one or more amino acid(s) and/or cyclodextrins and/or isotonicizing agents, as listed

above, which have been sterilized separately earlier and the blend is filled in suitable container to obtain active compound solution after reconstitution with vehicle or solvent.

The dissolution of the powder for reconstitution before the administration can be brought about both by addition of a solution, which is suitable for this purpose, into the container containing the powder and by addition of the powder to a suitable solution, or by a combination of procedures of these types.

The composition of the powder for reconstitution can likewise vary very widely, depending on the composition of the solution which is used for the dissolution.

It can vary from pure active compound to a powder for reconstitution which contain all the constituents which are to be administered, apart from water.

The invention likewise relates to combinations of powder for reconstitution with solutions containing active compound, which are converted into the infusion solutions according to the invention before the administration.

The invention also includes concentrates and suspensions which are converted into the solutions according to the invention before the administration.

It is possible in this context for these concentrates and suspensions to have various compositions. One possibility would be that which requires merely the addition of water for dilution or dissolution in order to prepare the infusion solutions according to the invention.

The invention also related to other presentations or combinations of presentations which finally result in the infusion solutions according to the invention-and this irrespective of the procedure.

The container into which lyophilizates, concentrates and other presentations such as, for example, suspensions, are dispensed can consist both of glass and of plastic. In this connection, the container materials can contain substances which confer a particular protection on the contents, such as, for example, a protection from light or a protection from oxygen.

Compositions of the present invention can also be prepared by processes known in the art, including by simple admixture, with agitation as appropriate, of the ingredients. Preferably an aqueous solution of the cyclodextrin compound is first prepared, and the benzoquinolizine is finely divided solid particulate form is added to that solution with agitation until it is fully dissolved. Where it is desired to prepare a buffered isotonic solution, for example for intravenous infusion, buffering agents and agents for adjustment of osmolality can be added at any stage but are preferably present in solution with the cyclodextrin compound before addition of the benzoquinolizine. Processes for preparing a composition of the invention, particularly one intended for parenteral use, are preferably conducted so as to provide a sterile product.

Compositions of the invention intended for parenteral administration are generally suitable for packaging and dispensing in conventional intravenous delivery bags and apparatus.

A contemplated composition can be dried, for example by spray drying, to form a reconstitutable powder. The powder can be dissolved in sterile water to reconstitute a parenterally deliverable composition as herein described.

In a method of the invention for treating or preventing infective disease, a composition as described above in a therapeutically or prophylactically effective daily dose is administered to a subject in need thereof. Such administration can be oral, parenteral or topical, but is preferably parenteral and more preferably by intravenous injection or infusion.

In a particular embodiment of the invention, a method for treating or preventing infective disease comprises (a) diluting a composition as described herein in a pharmaceutically acceptable liquid to form a diluted composition suitable for direct administration, and (b) administering the diluted composition in a therapeutically or prophylactically effective daily dose to a subject in need thereof. Preferably such administration is parenteral and the liquid in which the composition is diluted is a parenterally acceptable aqueous carrier, for example saline or a substantially isotonic buffered aqueous solution having a physiologically compatible pH.

As indicated above, a method of the invention is particularly useful where the infective disease arise through infection by one or more gram-positive bacteria. Where broader-spectrum antibacterial activity, extending to gram-negative bacteria, is required, a second antimicrobial drug can be administered in co-therapy, including for example coformulation, with the present composition. The second antimicrobial drug is selected to be effective

against target gram-negative bacteria. Such co-therapy and coformulation are embodiments of the present invention.

The second antimicrobial drug can illustratively be selected from aminoglycosides, cephalosporins, diaminopyridines, oxazolidinones, sulfonamides and tetracyclines. Among particular antimicrobial drugs of these and other classes, each of the following may illustratively be useful as the second antimicrobial drug according to an embodiment of the present invention: amikacin, cefixime, cefoperazone, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, imipenem, meropenem, eltapenem, chloramphenicol, clindamycin, colistin, domeclocycline, dexycycline, gentamicin, linezolid, mafenide, methacycline, minocycline, neomycin, oxyteracycline, polymyxin B, pyrimethamine, silver sulfadiazine, sulfacetamide, sulfisoxazole, tetracycline, tobramycin and trimethoprim.

The present invention also encompasses therapeutic and prophylactic methods involving administration of an antibacterial composition as described herein in co-therapy, including for example coformulation, with one or more drugs other than antibacterial drugs.

Therapeutic and prophylactic methods of the invention are useful for any subject in need thereof. The subject is preferably warm-blooded, more preferably mammalian, and most preferably human. However, a particular embodiment of the invention is a veterinary method of treating a non-human subject, for example a domestic, farm or zoo animal, having or at risk of infective disease, with a composition of the invention.

An appropriate dosage, frequently and duration of administration, i.e. treatment regimen, to be used in any particular situation will be readily determined by one of skill in the art without undue experimentation, and will depend, among other factors, on the particular benzoquinolizine compound(s) present in the composition, on the particular infective disease or condition to be treated or prevented, on the age, weight and general physical condition of the subject, and on other medication being administered to the subject. It is preferred that response to treatment according to the present method be monitored and the treatment regimen be adjusted if necessary in light of such monitoring.

Where the benzoquinolizine is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof, a daily dose for a human subject will generally be about 0.01 mg to 100 mg/kg/day, preferably 0.1 - 50 mg/kg/day. For an average 70 kg human, this would amount to 0.7 mg to 7 mg/day or preferably 7 mg - 3.5 mg/day of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof, administered as a single or divided dosage in a composition of the invention. For other benzoquinolizines, a daily dose that is therapeutically equivalent to the above dose ranges for S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof can be administered.

EXAMPLES

The following examples are provided for the purpose of illustrating the present invention but are not to be construed as limiting.

Test Example 1:

Abnormal Toxicity Study

Regulatory References: The study is designed to meet the recommendations of Indian Pharmacopoeia (IP) 1996, Appendix 2.2, Method B, Biological tests and determination, Test for abnormal toxicity; Government of India, Health and Family Welfare.

Dose Formulation: The composition is administered 'as such' at the dose of 120 mg/kg to individual mouse.

Test System And Management: Ten healthy (5 male and 5 female) Swiss mice, approximately 5-6 week old and weighing around 28-30 g, are placed at random in polypropylene cages, each cage containing 5 mice of the same sex. Throughout the experimental period animal room temperature and relative humidity is maintained between 22° C ± 3°C and 30 to 70% RH respectively. Illumination is controlled to give 12 hours light and 12 hours dark cycles (8.00 a.m. to 8.00 p.m.) each day. All mice have free access to Ultra-guard water (sterilised and cooled), and autoclaved standard pelleted laboratory animal diet. Autoclaved paddy husk is used as bedding and changed every alternate day.

Prior to final assignment to the study, all Swiss mice are subjected to veterinary examination and those in good state of health are selected.

Experimental Procedure:

Administration of test substance: Swiss mice are administered with the provided composition injection as a single intravenous dose. The composition is a clear solution of the test compound at a concentration of 9 mg/ml. The composition was administered intravenously 'as such' via tail vein of each mouse with the help of graduated 1 ml disposable syringe fitted with 26½G needle. Each mouse is given a volume calculated on the basis 120 mg/kg against respective body weight recorded prior to study initiation.

Observations made on the animals:

Clinical signs, Body Weight, Mortality

Test Example 2:

Stability Study

The compositions for injection obtained in Examples 1 & 2 are stored in a constant temperature incubator at 40°C for 3 months and are observed for physical clarity of solutions.

Test Example 3:

Solubility study with ß-cyclodextrin and hydroxypropyl ß-cyclodextrin

A study was conducted to examine the solubility of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[I,j] quinolizine-2-carboxylic acid in an

aqueous system containing ß-cyclodextrin (ß –CD) and hydroxypropyl ß –cyclodextrin (HP-ß-CD)

Aqueous solutions of (ß –CD) and (HP-ß-CD) at concentrations of 1,5,10 and 50 mg/ml were prepared. 1 ml of each of these solutions was added to an accurately weighed amount (about 20 mg) of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[I,j] quinolizine-2-carboxylic acid.

The amount of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[I,j] quinolizine-2-carboxylic acid dissolved at each concentration of CD and HP-ß-CD is shown in the following table:

ß –CD or HP-ß-CD mg/ml	Compound A mg/ml with		Compound B mg/ml with		Compound C mg/ml with		Compound D mg/ml with	
	ß –CD	HP-ß-CD	ß –CD	HP-ß-CD	ß –CD	HP-ß-CD	ß –CD	HP-ß-CD
0	0.04	0.04						
5	0.27	0.28						
10	0.53	0.55						
50		2.67						

Compound A:

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[I,j] quinolizine-2-carboxylic acid

Compound B:

RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[I,j] quinolizine-2-carboxylic acid

Compound C:

R-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[I,j] quinolizine-2-carboxylic acid

Compound D:

R-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[I,j] quinolizine-2-carboxylic acid arginine salt.

Test Example 4:

Solubility of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid arginine salt crystalline polymorph with hydroxypropyl ß -cyclodextrin (HP-ß-CD)

Aqueous solutions of (HP-ß-CD) at concentrations of 25, 60, 100 and 250 mg/ml were prepared. 1 ml of each of these solutions was added to 10 mg, 25 mg, 40 mg and 90 mg S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid arginine salt crystalline polymorph accurately weighed. The mixtures were shaken for about one minute to get clear solution. All the solutions were clear indicating full solubility of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid arginine salt at 0 hrs. These solutions were filtered through 0.2µm Whatman nylon filter. The filtered solutions were tightly

covered with polyfilm. The test tubes containing the solutions were mounted on a stand and kept on a mechanical shaker at 150 rpm for 6 hours and then upto 24 hours without shaking.

All solutions remained clear at 24 hrs. The pH of the solutions after 24 hours is shown in the table.

HP-ß-CD (mg/ml)	S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid arginine salt (mg/ml)	pH at 24 hrs.
25.0	10	7.62
60.0	25	7.75
100.0	40	7.82
250.0	90	7.97

Example 1

Preparation of a solution containing S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid arginine salt.

To 80 ml of water for injection, previously rendered inert with nitrogen gas sparging, is added and dissolved 1.0g L-arginine, 0.9g S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid arginine salt, and the volume made up to 100 ml with water for injection. The solution thus obtained is filtered

through membrane filters, filled in bottles and sterilised in an autoclave at 121°C for 20 minutes.

The pH of the solution is 9.37

In the abnormal toxicity study the solution is found to comply with the requirements.

The solution remains clear after keeping for 3 months at 40°C without the pH being modified.

The solution reduced vain irritation and also blocked any progression to cause severe phlebitis in contrast to the solution prepared from the corresponding sodium salt of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid

Example 2

Preparation of a solution containing S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid arginine salt rendered isotonic with sodium chloride.

To 80 ml of water for injection, previously rendered inert with nitrogen gas sparging, is added and dissolved 1.0g L-arginine, 0.9g S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1- oxo - 1H, 5H - benzo [i,j] quinolizine-2-carboxylic acid arginine salt, 0.67 g sodium chloride and the volume made up to 100 ml with water for injection. The solution thus obtained is filtered through membrane filters, filled in bottles and sterilised in an autoclave at 121°C for 20 minutes.

The pH of the solution is 9.75

In the abnormal toxicity study the solution has found to comply with the requirements.

The solution remains clear after keeping for 3 months at 40°C without the pH being modified.

The solution reduced vain irritation and also blocked any progression to cause severe phlebitis in contrast to the solution prepared from the corresponding sodium salt of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid

Examples 3, 4, 5, 6:

Preparations of solutions containing S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1- oxo - 1H, 5H - benzo [i,j] quinolizine-2-carboxylic acid arginine salt with various concentrations of L-arginine .

According to the conventional method of manufacturing as described in Example 1 aqueous solutions for injections having the following formulations were prepared.

Ingredients	Example			
	3	4	5	6
S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1- oxo - 1H, 5H - benzo [i,j] quinolizine-2-carboxylic acid arginine salt	0.9g	0.9g	0.9g	0.9g
L-arginine	0.30g	0.375g	0.45g	0.60g

water for injection	q.s. to 100ml	q.s. to 100ml	q.s. to 100ml	q.s. to 100ml
pH	9.04	9.06	9.19	9.28
Clarity	Clear	Clear	Clear	Clear

Example 7: Preparation of lyophillised formulation

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt (9% w/v), L-arginine (13%w/v) and mannitol (4% w/v) are dissolved in water for injection. After sterilisation filtration the solution is dispensed into vials, 10 ml each and then freeze-dried by a conventional method to obtain a freeze-dried preparation.

The preparation is reconstituted with 10 ml water for injection. The resulting solution is clear.

Example 8: Preparation of powder formulation

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid arginine salt (40.91%w/w) & L-arginine (59.09% w/w) are mixed & then aseptically filled with 2.2g powder mixture in each of 10 ml vials.

The preparation is reconstituted with 10 ml water for injection. The resulting solution is clear.

Example 9: Preparation of concentrated solution for injection

Preparation of a solution containing S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1- oxo - 1H, 5H - benzo [i,j] quinolizine-2-carboxylic acid arginine salt according to the conventional method concentrate solution for injection which can be used on further dilution with compatible intravenous fluids solution having the following formulation is prepared. To 5 ml propylene glycol previously rendered inert with nitrogen gas sparging is added and dissolved 2.0g polysorbate-80, 0.2g L-arginine, 0.9g S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1- oxo - 1H, 5H - benzo [i,j] quinolizine-2-carboxylic acid arginine salt, and the volume made up to 10 ml with water for injection. The solution thus obtained is filtered through membrane filters and filled in bottles.

The pH of solution is 8.90

The solution remains clear after keeping for 3 months at 40°C without the pH changing value.

Example 10:

Preparation of solution containing S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1- oxo - 1H, 5H - benzo [i,j] quinolizine-2-carboxylic acid arginine salt crystalline polymorph with hydroxypropyl B-cyclodextrin and rendered isotonic with sodium chloride.

To 90 ml of water for injection, previously rendered inert with nitrogen gas sparging, was added and dissolved 2.50 g hydroxypropyl B-cyclodextrin, 0.9 g S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1- oxo - 1H, 5H - benzo [i,j] quinolizine-2-carboxylic acid arginine salt crystalline polymorph, 0.80 g sodium chloride and the volume made upto 100 ml with water for injection. The solution thus obtained was filtered through membrane filters, filled in bottles and sterilized in an autoclave at 121 °C for 20 minutes.

The pH of the solution was 7.89.

The clarity of the solution was clear.

Example 11

Preparation of solution containing RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1- oxo - 1H, 5H - benzo [i,j] quinolizine-2-carboxylic acid arginine salt with hydroxypropyl B-cyclodextrin and rendered isotonic with sodium chloride.

To 90 ml of water for injection, previously rendered inert with nitrogen gas sparging, was added and dissolved 0.293 g arginine, 6.0 g hydroxypropyl B-cyclodextrin, 0.6 g RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1- oxo - 1H, 5H - benzo [i,j] quinolizine-2-carboxylic acid arginine salt and 0.70 g sodium chloride. The volume was made upto 100 ml with water for injection. The solution thus obtained was filtered through membrane filters, filled in bottles and sterilized in an autoclave at 121 °C for 20 minutes.

The pH of the solution was 7.60.

The clarity of the solution was clear.

Example 12:

Preparation of solution containing S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1- oxo - 1H, 5H - benzo [i,j] quinolizine-2-carboxylic acid with arginine and hydroxypropyl B-cyclodextrin, and rendered isotonic with sodium chloride.

Dated this 30th day of December 2002

DR N J de SOUZA

DIRECTOR-R&D